CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761143
Link to EDR	Link
Submission Date	07/08/2019
Submission Type	Priority
Proposed Brand Name	(b) (4)
Generic Name	Teprotumumab (HZN-001, RO4858696)
Dosage Form and Strength	500 mg teprotumumab lyophilized powder in a single-dose vial to prepare 50 mg/mL solution
Route of Administration	Systemic: Intravenous infusion
Proposed Indication	For the treatment of active Thyroid Eye Disease (TED)
Applicant	Horizon Therapeutics Ireland DAC
Associated IND	IND 112952
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1. EXECUTIVE SUMMARY

This is a 351(a) BLA submission for [redacted] (b) (4) which is a single-dose vial of 500 mg teprotumumab (HZN-001, RO4858696) lyophilized powder and the proposed indication is for the treatment of Active Thyroid Eye Disease (TED). The proposed teprotumumab dosing regimen is an initial dose of 10 mg/kg as an intravenous (IV) infusion (50 mg/mL teprotumumab solution) followed by seven IV infusions of 20 mg/kg every three weeks (Q3W) after the initial dose, i.e., total of 8 IV infusions Q3W. The proposed teprotumumab dosing regimen was evaluated in one Phase 2 and one Phase 3 study. Teprotumumab has been granted Fast Track, Breakthrough Therapy, and Orphan Drug designations by the FDA for the proposed indication.

The clinical pharmacology review focuses on the proposed teprotumumab dosing regimen for the proposed indication, characterization of teprotumumab PK based on Population (Pop) PK analyses, exposure-response (E-R) analyses for safety and efficacy, and the proposed drug product labeling.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the relevant clinical pharmacology information provided by the Applicant in BLA 761143 for teprotumumab and recommends approval of this BLA.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness is derived from one Phase 2 study (Study TED01RV) and one Phase 3 study (Study HZNP-TEP-301). Both studies were randomized placebo-controlled studies that evaluated the safety and efficacy of the proposed teprotumumab dosing regimen in patients with active TED.
General dosing instructions	The proposed teprotumumab dosing regimen is an initial IV infusion of 10 mg/kg teprotumumab followed by seven IV infusions of 20 mg/kg teprotumumab Q3W after the initial dose.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The Applicant has not proposed dose adjustments based on any intrinsic or extrinsic factors. The Applicant's proposal of no dosage adjustments in any patient subgroup (e.g., renal or hepatic impairment) is acceptable.
Labeling	Within the clinical pharmacology sections of drug product labeling, the Applicant proposes to include information that is mainly derived from a Pop PK report: Horizon-PopPK-001. Based on the current labeling guidance document and the review of the Pop PK report, the review team has recommended revisions to the Applicant's proposed labeling language. See Section 2.4.
Bridge between the to-be-marketed and clinical trial formulations	A bridging PK study between the to-be-marketed and clinical trial formulation is not warranted since teprotumumab is given by IV injection and the clinical trial formulation used in the clinical studies of TED patients is the same as the to-be-marketed formulation.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The proposed drug product is 50 mg/mL teprotumumab solution for IV infusion for the treatment of active TED. Teprotumumab is a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody against Insulin-like growth factor 1 receptor (IGF-1R). Blocking of IGF-1R signaling by teprotumumab is postulated to modify the downstream inflammatory/autoimmune pathophysiology that underlies the active TED phase. The final to-be-marketed product is derived from a Chinese hamster ovary (CHO) cell line.

Rationale for Dose Selection

The proposed teprotumumab dosing regimen is an initial IV infusion of 10 mg/kg followed by seven IV infusions of 20 mg/kg Q3W after the initial dose. The Applicant's rationale for the proposed teprotumumab dosing regimen is that this regimen is expected to produce > 90% saturation of target-mediated clearance of teprotumumab in TED patients. This is based on PK analysis of data from a dose-ranging Phase 1 study (Study BO19373) in oncology patients (dose range: 1 to 16 mg/kg).

Overall, the collective findings from a Pop PK analysis conducted by the Applicant from Study B019373 suggest that the proposed teprotumumab regimen is expected to produce > 90% saturation of target-mediated clearance of teprotumumab in TED patients. However, the Applicant has not submitted IGF-1 levels or estimated IGF-1R saturation levels in TED patients. In addition, the Applicant has not provided any IGF-1R/IGF-1 levels vs. efficacy response analysis that suggest a link between the saturation levels of IGF-1R by teprotumumab and its efficacy in TED patients.

Regarding the proposed initial dose of 10 mg/kg, the Applicant indicated that this dose was selected for patient tolerability. At the time of this review, during the clinical development program for TED, the Applicant did not conduct any dose-ranging studies nor evaluated the efficacy, safety, tolerability, and PK of teprotumumab following re-treatment with the proposed dosing regimen (i.e., more than 8 IV injections beyond 24 weeks). In addition, the Applicant did not provide justification for the proposed weight based dosing regimen nor the treatment duration in TED patients. However, the proposed teprotumumab dosing regimen was evaluated in one Phase 2 Study TED01RV and one Phase 3 Study HZNP-TEP-301 conducted in TED patients and the efficacy and safety findings from these studies were deemed to support the proposed regimen (see the Medical Officer's review).

Characterization of Systemic PK

Characterization of systemic PK of teprotumumab in TED patients was derived by the Applicant based on a Pop PK approach. The Pop PK analyses relied on pooled sparse teprotumumab PK data from 84 patients enrolled in two aforementioned clinical studies in TED patients (Phase 2 Study TED01RV and Phase 3 Study HZNP-TEP-301) and intensive PK data from 36 patients with advanced solid tumors, non-Hodgkin's lymphoma, or Hodgkin's lymphoma enrolled in the Phase 1 Study BO19373. However, the review of the supporting bioanalytical methods for Study TED01RV indicated that the PK samples collected from Study TED01RV were analyzed outside the established long-term stability period.

Therefore, the PK data from this study were excluded from the Pop PK analyses by the Clinical Pharmacology review team for purposes of deriving the post-hoc PK parameter estimates for product labeling. The Applicant conducted their Pop PK and E-R analyses using the PK data from Study TED01RV.

To further investigate the potential consequence of the PK sample stability related issue, additional Pop PK analyses were performed by the Clinical Pharmacology review team with and without the PK data from Study TED01RV. The findings from this additional analysis suggested no significant impact (<6% difference) on the PK estimates. Therefore, for the purposes of only conducting E-R analyses, the PK data from Study TEDRV01 were retained by the Clinical Pharmacology review team. Systemic teprotumumab PK in TED patients are summarized below.

Post-hoc mean (± standard deviation) PK exposure estimates at steady-state (week 21 to week 24) in 40 patients who were enrolled in Study HZNP-TEP-301 and received an initial intravenous infusion of 10 mg/kg teprotumumab, followed by infusions of 20 mg/kg teprotumumab Q3W are:

Area under the concentration curve (AUC_ss)= 138 (± 34) mg*hr/mL
Peak teprotumumab concentrations (Cmax_ss) = 632 (± 139) µg/mL
Trough teprotumumab concentrations (Cmin_ss) = 176 (± 56) µg/mL

Distribution: From the Pop PK analysis, the mean (± SD) of simulated estimates for the central volume of distribution, peripheral volume of distribution, and inter-compartment clearance at steady-state were 3.26 (± 0.87) L, 4.32 (± 0.67) L, and 0.74 (± 0.16) L/day, respectively.

Elimination: From the Pop PK analysis, the mean (± SD) of simulated estimates for teprotumumab clearance and the elimination half-life were 0.27 (± 0.08) L/day and 20 (± 5) days, respectively.

Metabolism: Metabolism of teprotumumab has not been fully characterized. However, teprotumumab is expected to undergo metabolism via proteolysis.

Specific Populations

Age, Sex, Racial Groups, and Weight: Pop PK analysis suggests that age (18-80 years old), race (103 White patients, 10 Black patients and 3 Asian patients), and weight (45.8-168.7 kg) had no effect on teprotumumab PK. Simulated Cmax estimates were 15% higher in female patients compared to male patients, however, simulated AUC estimates were similar.

Patients with Hepatic or Renal Impairment: Pop PK analysis in TED patients with mild or moderate renal impairment (measured based on creatinine clearance (CL_{CR}) estimates from 30 to 89 mL/min estimated by Cockcroft-Gault Equation) showed no significant change in the teprotumumab PK compared to TED patients with normal renal function (CL_{CR} > 89 mL/min). Teprotumumab PK has not been evaluated in patients with hepatic impairment and the effect of hepatic impairment on the PK of teprotumumab is unknown.

Immunogenicity

Immunogenicity testing was performed by screening anti-teprotumumab antibodies (ADAs) in serum samples collected from Studies TED01RV and HZNP-TEP-301. However, the ADA assay used for evaluating samples from Study TED01RV was deemed unacceptable by the CMC/OBP review team due to a drug tolerance issue, i.e., drug tolerance level was not adequate. In Study HZNP-TEP-301, none of the 41 teprotumumab treated patients had detectable anti-teprotumumab antibodies in serum; however, one of the 42 patients treated with placebo had detectable anti-teprotumumab antibodies in all collected serum samples from that patient.

Exposure-Response Analysis for Efficacy and Safety

The primary efficacy endpoint for the Phase 2 and Phase 3 studies was proptosis of the eye(s). Overall, there appears to be no conclusive trend of exposure-PRR (proptosis responder rate) relationship in 83 patients with TED from clinical studies HZNP-TEP-301 and TED01RV.

The primary adverse events of teprotumumab in TED patients were hyperglycemia and muscle spasm. No exposure-safety relationships were observed for hyperglycemia and muscle spasm using data collected from clinical studies HZNP-TEP-301 and TED01RV (n=84).

The exposure-response relationships for efficacy and safety should be interpreted with caution as it is based on a small number of patients from only one dosing regimen that was evaluated. The Applicant did not conduct any dose ranging studies.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen for teprotumumab is an initial IV infusion of 10 mg/kg teprotumumab followed by seven IV infusions of 20 mg/kg teprotumumab Q3W after the initial dose.

2.2.2 Therapeutic individualization

The Applicant has not proposed any therapeutic individualization. The available clinical pharmacology information does not warrant a need for therapeutic individualization.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Review Team's proposed specific additions to the Applicant's proposed labeling are in *blue* text and proposed deletions are marked as ~~*red strike out*~~ text.

Section	Recommendation
6.2 Immunogenicity	In a placebo-controlled study with (b) (4) one of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with (b) (4) had detectable levels of

(b) (4)	antidrug antibodies in serum. (b) (4) (b) (4)
12.1 Mechanism of Action	Teprotumumab-xxxx's mechanism of action in Thyroid Eye Disease patients has not been fully characterized. (b) (4) (b) (4)
12.2 Pharmacodynamics	Teprotumumab-xxxx exposure-response relationships and the time course of pharmacodynamic response are unknown.
12.3 Pharmacokinetics	The pharmacokinetics of teprotumumab-xxxx was described by a two compartment population PK model based on data from 40 patients with Active Thyroid Eye Disease receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg (b) (4) every 3 weeks in two clinical trials. Following this regimen, the mean (± standard deviation) estimates for steady-state area under the concentration curve (AUC), peak (Cmax), and trough (Ctrough) concentrations of teprotumumab-xxxx were 138 (± 34) mg•hr/mL, 632 (± 139) mcg/mL, and 176 (± 56) mcg/mL, respectively (b) (4) (b) (4) Distribution Following the recommended (b) (4) dosing regimen, the population PK estimated mean (± standard deviation) for central and peripheral volume of distribution of teprotumumab-xxxx were 3.26 (±0.87) L and 4.32 (± 0.67) L, respectively. The mean (± standard deviation) estimated inter-compartment clearance was 0.74 (± 0.16) L/day. (b) (4) (b) (4) Elimination

Following the recommended (b) (4) dosing regimen, the population PK estimated mean (± standard deviation) for the clearance of teprotumumab-xxxx was 0.27 (± 0.08) L/day and for the elimination half-life was 20 (± 5) days.

Metabolism

Metabolism of teprotumumab-xxxx has not been fully characterized. However, teprotumumab-xxxx is expected to undergo metabolism via proteolysis. (b) (4)

(b) (4)

Specific Populations

No clinically significant differences in the pharmacokinetics of teprotumumab-xxxx were observed following administration of (b) (4) based on patient's age (18-80 years), sex, race/ethnicity (103 White, 10 Black, and 3 Asian), weight (b) (4), mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min estimated by Cockcroft-Gault Equation), bilirubin levels (2.74-24.3 mcmol/L), aspartate aminotransferase (AST) levels (11-221 U/L), or alanine aminotransferase (ALT) levels (7-174 U/L). The effect of hepatic impairment on the pharmacokinetics of teprotumumab-xxxx is unknown.

(b) (4)

Drug Interactions

No studies evaluating the drug interaction potential of (b) (4) have been conducted.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Teprotumumab is a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody against Insulin-like growth factor 1 receptor (IGF-1R). Teprotumumab was originally being developed by a different sponsor for the treatment of a variety of solid tumors; however, the development program was terminated due to lack of efficacy. During the previous development program, the teprotumumab IV dosing regimens evaluated included 9 mg/kg QW (n=310) and 27 mg/kg Q3W (n=7) regimens in patients with recurrent or refractory sarcoma.

The proposed indication for teprotumumab in this submission is for the treatment of active TED. IGF-1R is postulated to play a key role in the underlying immunopathogenesis during active TED phase. TED is autoimmune orbital inflammatory condition and is also known as thyroid-associated ophthalmopathy, or Graves' ophthalmopathy. TED manifests with an active (dynamic) phase lasting up to 24 months, followed by an inactive (static) disease phase. Blocking of IGF-1R signaling by teprotumumab is believed to modify the downstream inflammatory/autoimmune pathophysiology that underlies active TED phase.

The proposed teprotumumab dosing regimen is an initial IV infusion of 10 mg/kg teprotumumab followed by seven IV infusions of 20 mg/kg teprotumumab Q3W after the initial dose. This proposed teprotumumab dosing regimen was evaluated in one Phase 2 Study TED01RV and one Phase 3 Study HZNP-TEP-301 conducted in TED patients. Information on the systemic PK of teprotumumab is derived from a Pop PK analysis of the same two studies. PK characteristics of teprotumumab are summarized in the table in Section 3.2.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Teprotumumab clinical pharmacology information is presented in table below.

Pharmacology	
Formulation	500 mg teprotumumab lyophilized powder in a single-dose vial to prepare 50 mg/mL solution
Mechanism of Action	Teprotumumab's mechanism of action in Thyroid Eye Disease patients has not been fully characterized.
Systemic Pharmacokinetics	
Healthy subjects	Not evaluated
Active TED Patients	Derived by relying on a Pop PK approach using pooled sparse teprotumumab PK data from 84 patients enrolled in two clinical studies in TED patients and intensive PK data from 36 patients with advanced solid tumors, non-Hodgkin's lymphoma, or Hodgkin's lymphoma enrolled in a Phase 1 study. The PK of teprotumumab was described by a two compartment PK model and the following are mean (±SD) estimates at steady state in TED patients receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg every 3 weeks: AUC_ss=131 (± 30.9) mg*hr/mL Cmax_ss= 643 (± 130) mcg/mL Cmin_ss= 157 (± 50.6) mcg/mL

Distribution	
Volume of Distribution at Steady State	Central compartment: 3.26 (SD=± 0.87) L Peripheral compartment: 4.32 (SD=± 0.67) L
Elimination	
Half-Life	19.9 (SD = ± 5.21) days
Total Clearance	0.27 (SD=± 0.08) L/day
Metabolism & Excretion	Metabolism of teprotumumab has not been fully characterized. However, free teprotumumab is expected to undergo metabolism via proteolysis.
Immunogenicity	
In Study HZNP-TEP-301, from the 42 patients treated with placebo, one patient had detectable levels of antidrug antibodies in serum samples collected at Day 1 and at Weeks 3, 9, and 24. In the same study, none of the 41 patients treated with teprotumumab had detectable level of antidrug antibodies in serum.	
In Vitro & In Vivo Drug Interaction Findings	
Since this is a monoclonal antibody, no drug-drug interaction studies were conducted.	

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The safety and efficacy of the proposed teprotumumab dosing regimen in active TED patients were evaluated in two randomized, placebo-controlled studies: Studies TED01RV and HZNP-TEP-301. These studies provide pivotal evidence of effectiveness for the proposed indication of treatment of active TED.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general active TED patient population.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

The available clinical pharmacology information does not warrant a need for therapeutic individualization based on intrinsic factors.

Population PK analysis suggests that age (18-80 years), race (103 white patients, 10 black patients, and 3 Asian patients), and weight (45.8-168.7 kg) had no effect on teprotumumab exposures. Simulated C_{max} estimates were 15% higher in female patients compared to male patients, however, simulated AUC estimates were similar.

With respect to renal impairment, findings from a Pop PK analysis suggest that in TED patients with mild or moderate renal impairment (measured based on creatinine clearance (CL_{CR}) estimates from 30 to 89 mL/min estimated by Cockcroft-Gault Equation), no significant change in the teprotumumab PK was observed compared to TED patients with normal renal function (CLCR > 89 mL/min). Effect of severe renal impairment on teprotumumab PK is unknown.

With respect to hepatic impairment, the effect of hepatic impairment on teprotumumab PK has not been evaluated. Pop PK analysis indicated that bilirubin (2.74-24.3 µmol/L), aspartate aminotransferase (AST) (11-221 U/L) and alanine aminotransferase (ALT) (7-174 U/L) had no notable relationship with the PK of teprotumumab.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

- The drug product is given via IV infusion; therefore, the issue of a food-drug interaction is not relevant.

- No drug-drug interaction studies were conducted in vitro or in vivo. However, drug-drug interactions are not expected based on CYP450, other metabolizing enzymes, or transporters, since teprotumumab's metabolism does not utilize these pathways.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Studies BO19373, TED01RV, and HZNP-TEP-301 evaluated the systemic PK of teprotumumab and utilized three different bioanalytical methods for quantifying teprotumumab in human serum. Review of these bioanalytical methods is summarized in the table below.

Study	**BO19373**	
Analyte/Assessment	Teprotumumab (RO4858696)	
Method	A sandwich ELISA method utilizing Streptavidin-coated plates was used with biotinylated recombinant human IGF receptor (IGFrbiotin) as a capture. Calibrators, controls, and samples were added to the plate. For detection, a polyclonal antibody that was previously modified with digoxigenin (MAB-DIG) was used followed by addition of anti-digoxigenin-HRP (anti-DIG-HRP) conjugate and tetramethyl benzidine (TMB).	
Validation Report	Validation report provided: Study 6131-589 - Addendum No. 1	☒ Yes ☐ No
	Validation report acceptable: Range: 25 ng/mL (LLOQ) to 1000 ng/mL (up to 1000 µg/mL with dilution) Notes: The effect of hemolysis or lipemia on quantification of teprotumumab was not characterized.	☒ Yes ☐ No
Performance Report	Performance report provided: REPORT NO. 1029622	☒ Yes ☐ No
	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable QC: 75 ng/mL, 500 ng/mL, 750 ng/mL	☒ Yes ☐ No
	Chromatograms provided	*NA*
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable Notes: Incurred sample re-analysis was performed in 5.2% of study samples, and 88% of the samples met the pre-specified criteria. It is generally recommended that 10% of study samples be used for ISR analysis.	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No

Study	**TED01RV**	
Analyte/Assessment	Teprotumumab (RV-001)	
Method	An ELISA method was used with Human IGF1R/CD221 Protein as a capturing agent. Calibrators, controls, and samples were added to the plate. For detection, anti-RV001-Biotin was used followed by incubations with SA-HRP and 1-Step™ Ultra TMB-ELISA Substrate. At the end ~2N sulfuric acid was added as stop solution.	
Validation Report	Validation report provided: 2165-006[1] and Addendum No. 1	☒ Yes ☐ No
	Validation report acceptable: Range: 76.3 ng/mL (LLOQ) to 1280 ng/mL	☒ Yes ☐ No
Performance Report	Performance report provided: REPORT NO. 2165-003	☒ Yes ☐ No
	Samples analyzed within the established stability period *Notes: The analytical report notes that PK samples for this study were not analyzed within the established long-term frozen storage stability period. The report notes that long-term frozen storage stability could not be achieved for the QC samples at low concentration as over-recovery was observed. Therefore, sample concentrations from samples at lower concentrations stored frozen for longer than 91 days should be considered estimates of exposure. The report also notes that given that incurred sample stability showed only a negligible mean increase in concentration following additional storage, the lack of stability at the QC low concentration has limited impact on the evaluation of incurred samples following approximately 17 to 18 months.*	☐ Yes ☒ No
	Quality control (QC) samples range acceptable QC: 154 ng/mL, 410 ng/mL, 1020 ng/mL	☒ Yes ☐ No
	Chromatograms provided	*NA*
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable *Notes: Since, PK samples collected from Study TED01RV were analyzed outside the established long-term stability period, PK data from this study were excluded from the Pop PK analysis for determining the PK parameters and for purposes of inclusion into labeling.*	☐ Yes ☒ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No
Study	**HZNP-TEP-301**	
Analyte/Assessment	Teprotumumab (HZN-001)	
Method	Electrochemiluminescent (ECL) method- standards, controls and test samples are incubated with monoclonal mouse anti-HZN-001 antibody followed by incubation with a different monoclonal Mouse Anti-HZN-001 antibody that has been conjugated with Sulfo-Tag. Detection was based on visualizing conjugate with MSD Read Buffer T (2X) and read on the MSD QuickPlex™ SQ 120.	
Validation Report	Validation report provided: AR138-C1133-17-0124	☒ Yes ☐ No
	Validation report acceptable: Range: 10 ng/mL (LLOQ) to 4000 ng/mL	☒ Yes ☐ No
Performance Report	Performance report provided: 138-C1133-17-0126	☒ Yes ☐ No

[1] Sample analysis was initially started using an analytical method validated under Study Number 2165-001; however, due to assay performance issues, a new method was validated under Study Number 2165-006.

	Samples analyzed within the established stability period *Note: For this specific analytical method, which is in use from January 2019, the Applicant notes that long-term storage 1, 3, 6, 12, and 18 months stability analysis is pending. The stability data submitted in support of Study BO19373 show at least 12 months of stability.*	*NP*
	Quality control (QC) samples range acceptable QC: 25 ng/mL, 800 ng/mL, 3000 ng/mL	☒ Yes ☐ No
	Chromatograms provided	*NA*
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable *Notes: The overall ISR passing rate was 77.1%*	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No

NA: Not applicable, NP: Not provided.

Anti-teprotumumab Antibodies in Human Serum: Refer to the CMC/OBP immunogenicity review for further details on the assays.

4.2 Clinical PK Assessments

The information on systemic PK of teprotumumab is derived using a population PK approach utilizing PK data from studies BO19373, TED01RV, and HZNP-TEP-301.

Study BO19373

Title: Multiple Ascending Dose (MAD) Phase 1 Study of the IGF-1R Antagonist R1507 *[Teprotumumab, RO4858696]* Administered as an Intravenous Infusion on QW and Q3W Schedules in Patients With Advanced Solid Tumors, Non-Hodgkin's Lymphomas, Or Hodgkin's Lymphoma.

This was an open-label Phase 1 dose-escalation study conducted in patients with advanced solid tumors, non-Hodgkin's Lymphomas or Hodgkin's Lymphoma. The primary objective of this study was to characterize the PK of teprotumumab, to determine the maximum tolerated dose (MTD) – if achieved – and to assess the effect of teprotumumab on tumor expression of IGF-1R in patients with advanced solid neoplasms. This study used teprotumumab drug products manufactured in CHO cell lines and SP2/0 cell lines. Given the proposed to-be-marketed drug product is manufactured in CHO cell lines, only the clinical pharmacology findings pertaining to the CHO cell line drug product is summarized below.

In total, 36 patients received teprotumumab as per one of the following two schedules:

- Every three weeks dosing (Q3W): 16 mg/kg (13 patients)
- Weekly dosing (QW): 3 mg/kg (3 patients), 6 mg/kg (13 patients), 9 mg/kg (7 patients)

Teprotumumab was administered via IV infusion over 90 minutes during the initial infusion and in the absence of any reaction, subsequent doses were administered over 60 minutes infusion. For PK assessments, blood samples were planned to be collected from both the treatment arms as follows:

- QW: Pre-dose and up to 72 hours post-dose on Week 1 and Week 7
  Pre-dose samples on Weeks 2, 3, 4, 8, and 10.

- Q3W: Pre-dose and up to 72 hours post-dose on Day (D) 1 of Q3W dosing cycles (C) 1 and 3
  Pre-dose samples on D8 & D15 C1 and on D1-2, D8-C3, and D1-C4.

PK assessments were performed based on teprotumumab serum levels using a Pop PK approach. Please see Section 4.3 for more information on the Pop PK analysis.

Exposure and additional PK parameter estimates were also derived from the available teprotumumab serum levels using non-compartmental analysis (NCA). The study report contained descriptive statistics of NCA findings, however, these findings are not presented in this review as this study was conducted in non-TED patients. Along the same line of reasoning, safety findings are also not described/discussed in this review.

It is noteworthy that during the conduct of this study, IGF-1 levels were assessed in this non-TED patient population across all the dose levels tested. The findings suggested that IGF-1 levels increased throughout the dosing interval, however, were highly variable and not correlated with the dose levels.

Study TED01RV

Title: A Multicenter, Randomized, Double-masked, Placebo-controlled, Efficacy and Safety Study of Teprotumumab (HZN-001), an Insulin-like Growth Factor-1 Receptor (IGF-1R) Antagonist Antibody (Fully Human), Administered Every 3 Weeks (Q3W) by Intravenous (IV) Infusion in Patients Suffering from Active Thyroid Eye Disease (TED).

This was a Phase 2 study and the primary objective was to investigate the efficacy, safety, and tolerability of teprotumumab in active TED patients. The study enrolled 88 patients and they were randomly assigned (stratified by smoking status) in a 1:1 ratio to receive one of the following two treatments:

- An initial IV dose of 10 mg/kg followed by seven IV infusions of 20 mg/kg Q3W after the initial dose
- Placebo Q3W via IV infusion.

Of the enrolled patients, 87 patients received at least 1 dose of teprotumumab (n=42) or placebo (n=45).

Please see the Medical officer's review for complete information on the enrolled patients' disposition and for the safety and efficacy related findings. Selected efficacy, safety, PK, and immunogenicity related information are discussed below.

Efficacy: The efficacy endpoints from this study included in the Applicant's exposure-responses analysis (Section 4.4) are the response rate at Week 24 for proptosis, diplopia, and Clinical Activity Score (CAS). Proptosis was measured based on Hertel values (a distance measurement in millimeter (mm) from the lateral orbital rim to the corneal apex) for study eye and responders were defined as patients with the decrease of ≥2 mm. For diplopia assessment, score was defined as 0 =no diplopia; 1=intermittent

(diplopia in primary position of gaze, when tired or when first awakening); 2=inconstant (diplopia at extremes of gaze); 3=constant (continuous diplopia in primary of reading position). Diplopia responder was defined as a patient who had a decrease ≥1 grade. CAS was measured on a 7-point scale comprising of two patient-reported outcomes and five clinician-reported/assessed outcomes. CAS responders were defined as patients with decrease of ≥2 points. CAS is calculated by assigning 1 point to each of the following items and then calculating sum of these points:

1. Spontaneous orbital pain
2. Gaze-evoked orbital pain
3. Eyelid swelling that was considered to be due to active (inflammatory phase) Graves' Ophthalmopathy (GO)
4. Eyelid erythema
1. Conjunctival redness that was considered to be due to active (inflammatory phase) GO (ignore "equivocal" redness)
5. Chemosis
6. Inflammation of caruncle or plica

Safety: Overall, the four most common treatment-emergent adverse events (TEAEs) reported in at least 5% of patients in either group were nausea, muscle spasms, fatigue, and diarrhea. In addition, hearing impairment was reported in three patients in the teprotumumab group. Except for fatigue, these events were reported in a higher proportion of patients in the teprotumumab group compared to the placebo group. In addition, hyperglycemia was reported in higher proportion of patients who received teprotumumab compared to the patients receiving placebo. Muscle spasm and hyperglycemia events were included in the Applicant's exposure-response analysis (Section 4.4).

Pharmacokinetic Assessments: Whole blood samples were collected to determine teprotumumab serum concentrations at the following time points: pre- and post-infusion at Weeks 0, 3, and 9 and single samples at Weeks 1, 4, and 24. In total, 370 PK samples were collected from 43 patients and serum teprotumumab levels were used for the Pop PK modeling analysis (Section 4.3).

Immunogenicity: Using a stepwise anti-drug antibody (ADA) analysis approach, immunogenicity of teprotumumab was assessed in serum samples prior to dosing (baseline), at Weeks 3, 9, 24, and as applicable at Weeks 36 and 72. Two teprotumumab-treated patients confirmed positive for the presence of ADA. One patient was positive at Week 3 and was negative at subsequent timepoints. A second patient was positive at baseline and at Week 72. The available limited PK information suggested no notable differences between PK profiles of two ADA-positive patients to those of ADA-negative patients. The Review team recommends against including the immunogenicity findings from this study in the drug product labeling as the teprotumumab ADA assay used for evaluating samples in this study had a drug tolerance issue. Please see the CMC/OBP immunogenicity review for more information on the drug tolerance issue with the ADA assay used in this study.

Study HZNP-TEP-301

Title: A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Active Thyroid Eye Disease Short title: Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC)

This was a Phase 3 study and the primary objective was to evaluate the effect of teprotumumab versus placebo on the proptosis responder rate (i.e., percentage of patients with a ≥2 mm reduction from baseline in proptosis in the study eye without deterioration [≥2 mm increase] of proptosis in the fellow eye) at Week 24. The study enrolled 83 patients and they were randomly assigned (stratified by smoking status) in a 1:1 ratio to receive one of the following two treatments:

- An initial IV dose of 10 mg/kg followed by seven IV infusions of 20 mg/kg Q3W after the initial dose
- Placebo Q3W via IV infusion.

Of the enrolled patients, 79 patients completed the treatment.

Please see the Medical officer's review for complete information on the enrolled patients' disposition and for the safety and efficacy related findings. Selected efficacy, safety, PK, and immunogenicity related information are discussed below.

Efficacy: The efficacy endpoints from this study that were used in the Applicant's exposure-response analysis (Section 4.4) are the response rate at Week 24 for proptosis, diplopia, and Clinical Activity Score (CAS). The criteria for determining response rates for these efficacy endpoints were similar to the criteria used in Study TEDRV01, which are detailed above.

Safety: Treatment induced adverse events that occurred more commonly in the teprotumumab group compared to the placebo group included muscle spasms, alopecia, nausea, fatigue, dysgeusia, dry skin, dizziness, hearing impairment, and amenorrhoea. In addition, hyperglycemia was reported in two patients who received teprotumumab compared to no patients receiving placebo. Muscle spasm and hyperglycemia events were included in the Applicant's exposure-response analysis (Section 4.4).

Pharmacokinetics Assessments: Whole blood samples were collected from the 40 patients receiving teprotumumab at the following time points: pre- and post-infusion at Weeks 0, 3, and 9 and single samples at Weeks 1, 4, and 24. Serum teprotumumab levels from these samples were used for the Pop PK modeling analysis (Section 4.3).

Immunogenicity: Using a stepwise anti-drug antibody (ADA) analysis approach, immunogenicity of teprotumumab was assessed in serum samples prior to dosing (baseline), at Weeks 3, 9, 24, and as applicable at Weeks 36 and 72. None of the teprotumumab-treated patients had detectable levels of ADA in serum.

4.3 Population PK Analysis

The goal of population PK (popPK) analysis was to develop a population PK model to assess sources of variability (intrinsic and extrinsic covariates) in teprotumumab PK in TED patients.

The population PK model included 3 clinical trials, comprising 36 oncology patients and 83 patients with TED. The baseline population characteristics in the popPK model evaluation dataset is provided in Table 1. The popPK analysis was conducted by the Applicant. The PK of teprotumumab was characterized by a two-compartment PK model with first-order elimination from the central compartment and redistribution from the peripheral compartment. Disposition of teprotumumab was modelled in terms of clearance (CL), volume of distribution for the central compartment (Vc), inter-compartmental clearance (Q), and volume of distribution for the peripheral compartment (Vp). Between-patient variability (BSV) was included on the CL, Vc, Q, and Vp. A log-additive residual model was selected based on model diagnostics.

Table 1: Baseline Population Characteristics in the PopPK Model Evaluation Dataset

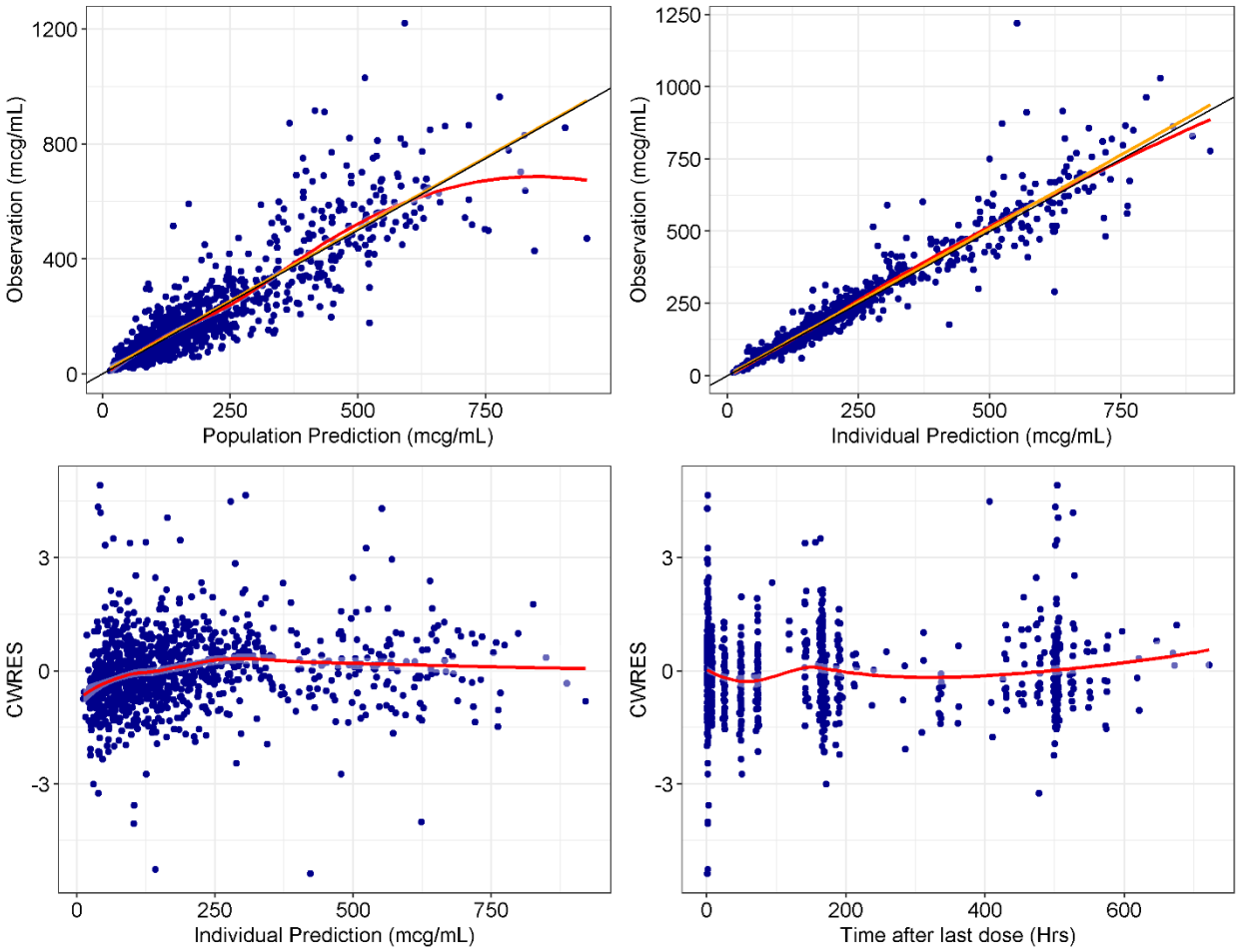
Characteristics	**Evaluation Dataset**	
No. of subjects	119	
No. of samples	1063	
Continuous Covariates (abbreviation, unit)	**Median [min, max]**	**N**
Age (AGE, years)	52 [18-80]	119
Weight (WT, kg)	74.8 [45.8-169]	119
Baseline bilirubin (BIL, µmol/L)	8 [2.74-24.3]	116
Baseline aspartate aminotransferase (AST, U/L)	21 [11-221]	118
Baseline alanine aminotransferase (ALT, U/L)	20 [7-174]	119
Baseline creatinine (Creatine, mmol/L)	0.814 [0.441-1.8]	119
Baseline creatinine clearance (CRCL, mL/min)	104 [41.6-278]	119
Categorical Covariates (abbreviation, group)	**N**	**N**
Race (RACEN, White/Asian/Black/Other)	103/3/10/3	119
Sex (SEX, Male/Female)	47/72	119
Smoking status (SMOK, Missing/Non-User/User)	36/63/20	119
Ethnicity (ETH, Missing/Non-Hispanic/Hispanic)	2/113/4	119
Disease (DIS, Oncology/TED)	36/83	119

Source: Applicant's popPK report, Page 24, Table 4

The Applicant's proposed PK model (Final popPK Model) has been evaluated by the reviewer. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 1). Prediction-corrected

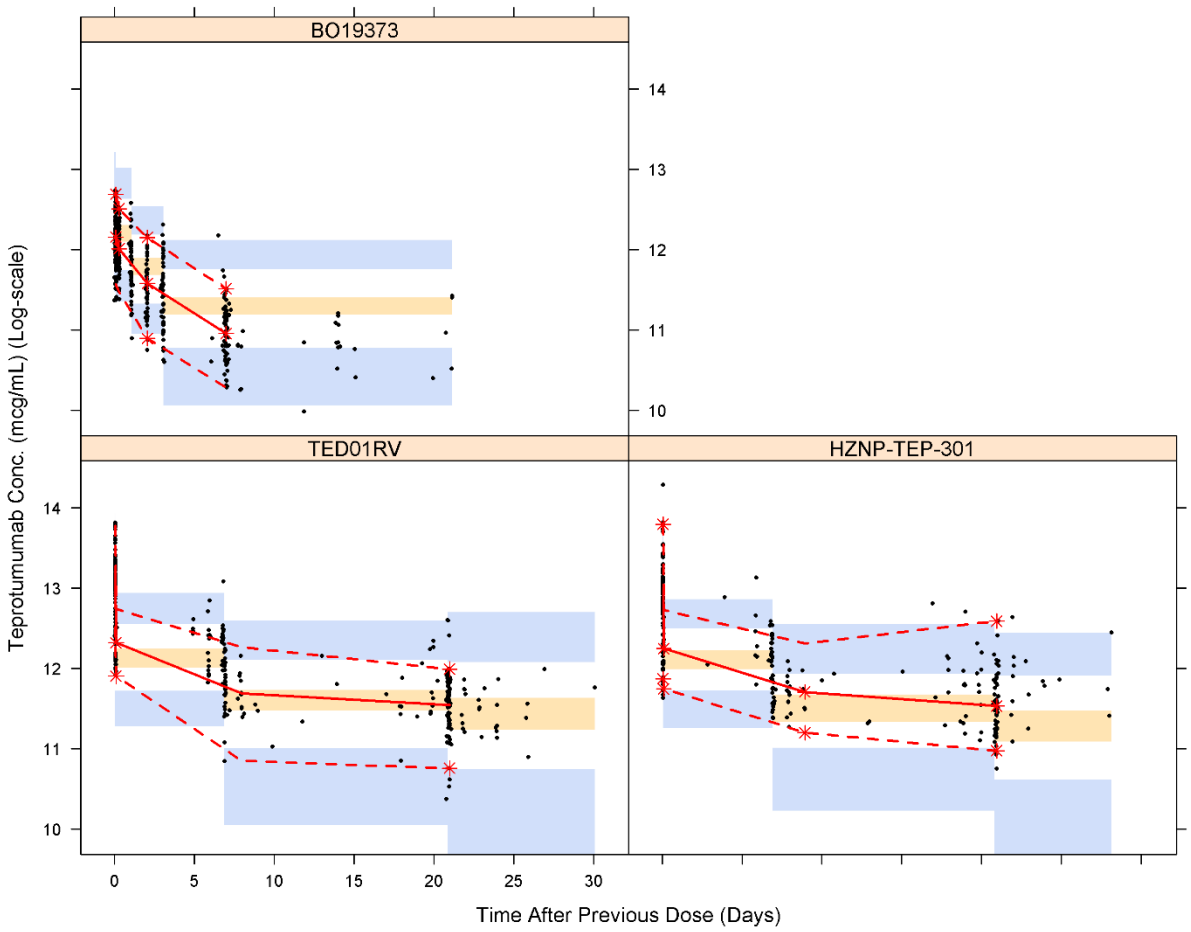
visual predictive check showed that the final model adequately described the observed PK profile of teprotumumab in each clinical trial (Figure 2). The shrinkage in the eta residual is 4% for CL and 7% for Vc.

Figure 1: Goodness of Fit Plots of the Final PopPK Model



Source: Reviewer's Analysis based on "pkinput.csv"

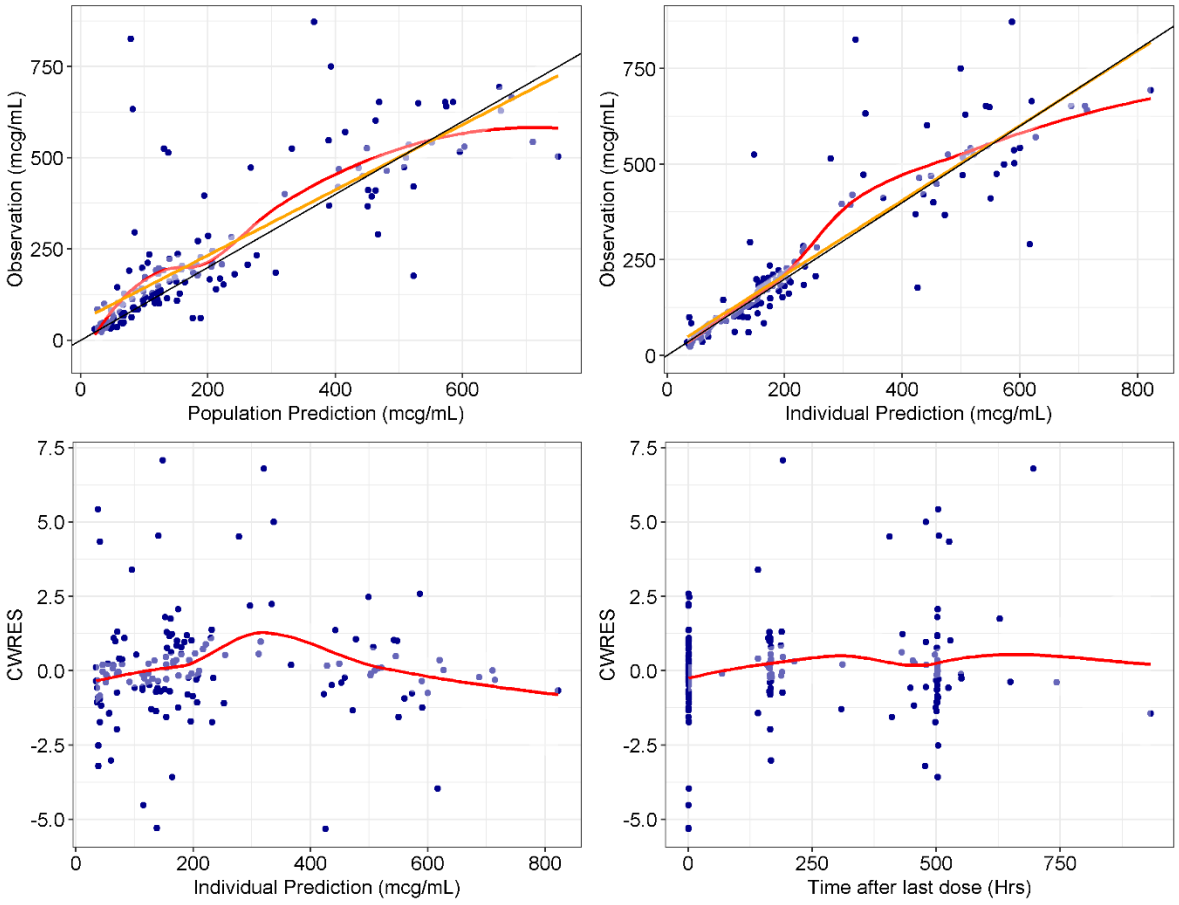
Figure 2: Visual Predictive Checks of Teprotumumab Concentration-Time Data Stratified by Study



Source: Reviewer's Analysis based on "pkinput.csv"

The prediction of popPK model was also evaluated through external validation. The external validation dataset was comprised of 19 TED patients contributing a total of 150 new teprotumumab concentration records. A good agreement was observed between the predicted concentrations and the observed concentrations. Figure 3 shows that teprotumumab predicted concentrations are consistent with observed concentrations.

Figure 3: Goodness of Fit Plots of the Final External Validation PopPK Model



Source: Reviewer's Analysis based on "pkinput.csv"

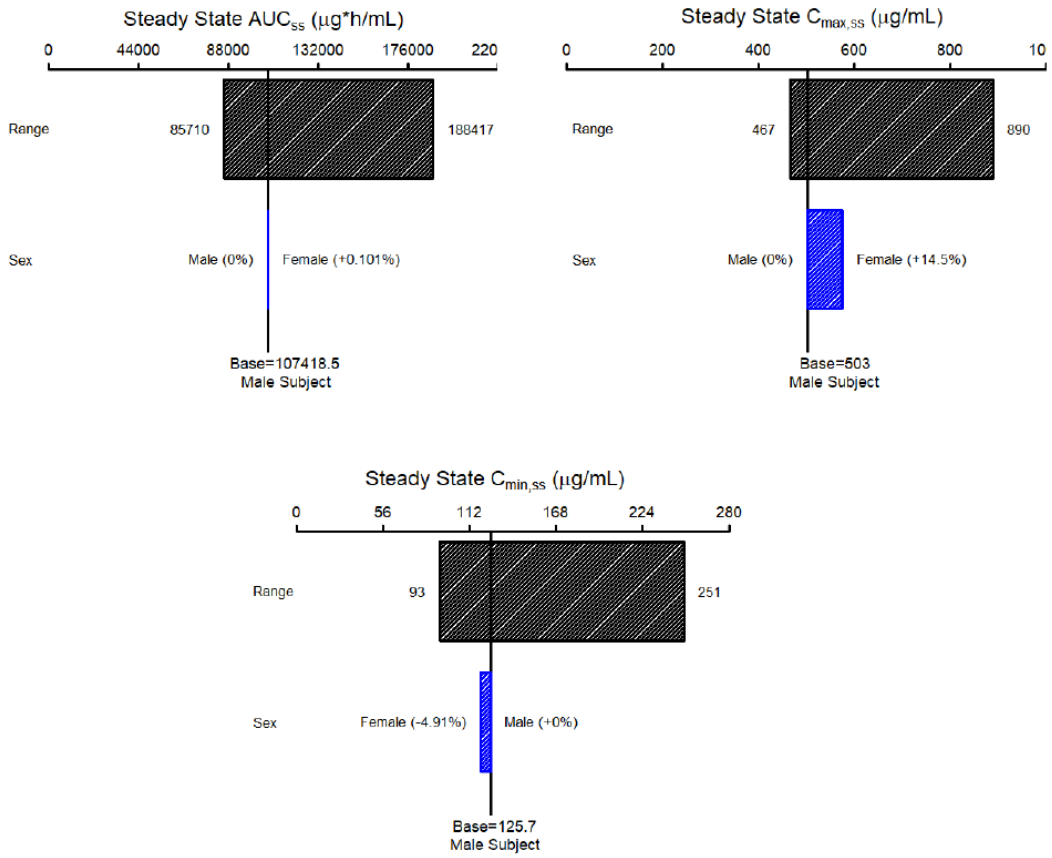
The influence of continuous and categorical covariates was tested for their statistically significant impact on PK parameters in the model. Covariates were selected based on known or hypothetical factors that could affect the PK. These covariates include baseline age, body weight, sex, ethnicity, race, smoking status, bilirubin, alanine aminotransferase, aspartate aminotransferase, and creatinine clearance. Testing of the covariates one-at-a-time using a stepwise forward addition method showed that the effect of sex and weight on Vc were significant ($p<0.01$). The full popPK model included all significant covariate relationships. Covariates were then excluded from the full popPK model using a backward elimination method (a change in likelihood ratio >10.83 for 1 parameter ($p<0.001$)). Weight on Vc was removed in the backward elimination process. Parameter estimates of final covariate model including significant covariates were provided in Table 2. The final model included effects of sex on Vc. The effects of sex on the teprotumumab exposure (AUC and C_{max} at steady state) are illustrated in the forest plot (Figure 4). Overall, female patients had 0.101% higher AUC_ss, 14.5% higher Cmax_ss, and 4.91% lower Cmin_ss compared to male patients. The effect of sex on teprotumumab exposure was not considered clinically relevant.

Table 2: Parameter Estimates of the Final PopPK Model

Parameter	Parameter Description	Population Estimate (%SE)	Inter-Individual Variability (%SE)
$exp(\theta_1)$	Central clearance, CL (L/day)	0.334 (1.65%)	43.0 (15.3%)
$exp(\theta_2)$	Central volume, V_c (L)	3.94 (3.98%)	27.7 (15.1%)
$exp(\theta_3)$	Inter-compartmental clearance, Q (L/day)	0.859 (0.557%)	47.8 (19.6%)
$exp(\theta_4)$	Peripheral volume, V_p (L)	4.21 (0.792%)	25.4 (39.4%)
θ_5	Influence of Sex on V_c	-0.191 (-14.7%)	—
$\omega^2_{CL,Vc}$	covariance between CL and V_c	0.0763 (19.5%)	
σ	Residual error (%)	18.0 (13.6%)	

Source: Applicant's popPK report, Table 5, Page 28

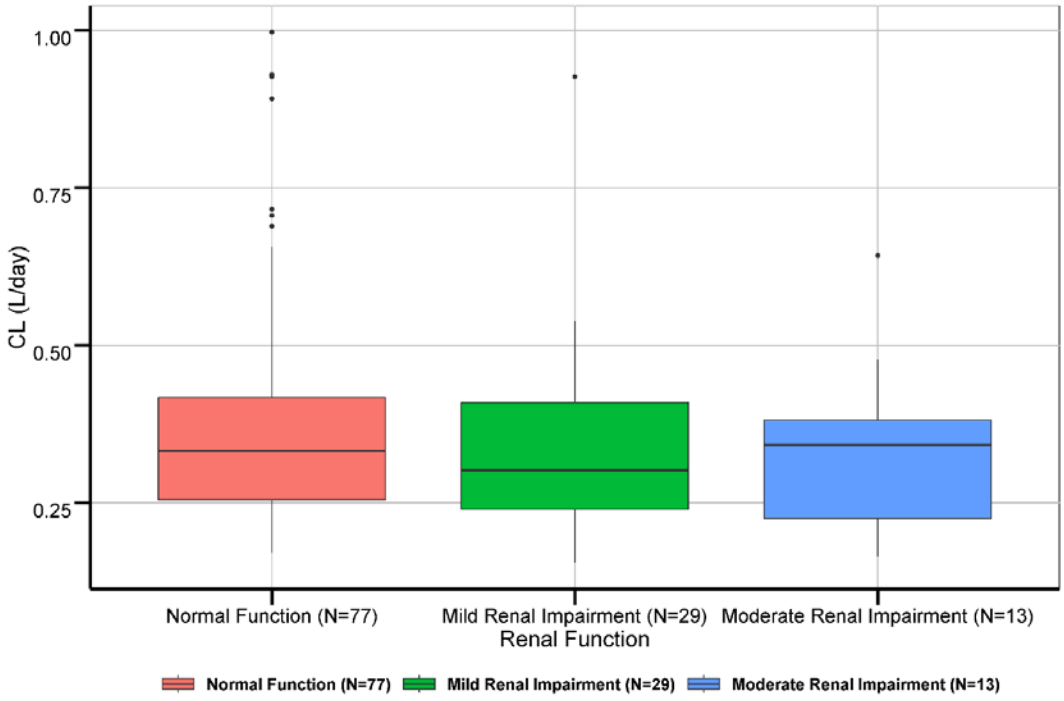
Figure 4: Covariate Effects on Teprotumumab Exposure (AUC_ss, Cmax_ss, Cmin_ss)



Source: Applicant's popPK report, Figure 11, Page 38

Other tested covariates were found to have no statistically significant effect on teprotumumab PK parameters. The Review team agrees with the Applicant's labeling claim that age (range: 18-80 years old), sex (47 male and 72 female patients), race (103 white patients, 10 black patients), body weight (range: 45.8-168.7 kg) have no clinically meaningful effect on teprotumumab PK. By mechanism, organ functions were not believed to have effect on teprotumumab exposure as teprotumumab is an antibody with molecular mass larger than 69 kDa. In the popPK analysis renal function indicator (creatinine clearance (range: 41.6-278 ml/min, estimated by Cockcroft-Gault Equation)) and liver function indicator (bilirubin (range: 2.74-24.3 µmol/L)) also were found to have no effect on teprotumumab PK parameters. The post-hoc clearance estimates were also similar between patients with mild (creatinine clearance (CL_{CR}) estimates from 60 to 89 mL/min estimated by Cockcroft-Gault Equation) (N=29) to moderate (creatinine clearance (CL_{CR}) estimates from 30 to 59 mL/min estimated by Cockcroft-Gault Equation) (N=13) renal impairment and patients with normal renal function.

Figure 5: Boxplots of Post-hoc Teprotumumab Clearance Across Renal Function



Source: Reviewer's Analysis based on "pkinput.csv"

Weight is not a statically significant covariate on clearance based on popPK analysis. Post-hoc estimated teprotumumab exposures by body weight (BW) quartiles are provided in Table 3. Mean teprotumumab exposures (AUC_ss, Cmax_ss, and Cmin_ss) observed in subjects within the lowest quartile of BW were 17.9%, 16.8%, and 9.36% lower, respectively, than subjects in the highest BW quartile. This analysis suggests even though BW is not a statistically significant covariate on CL, the exposure difference between patients with low BW and patients with high BW following the proposed BW-based dosing regimen is not expected to be clinically meaningful.

The observed PK data also showed that TED patients had a higher exposure compared with oncology patients. Post-hoc estimation showed that the mean teprotumumab AUC_ss, Cmax_ss, and Cmin_ss in oncology patients was 43%, 33.9%, and 53.7% lower, respectively, than in TED patients (Table 5). The mechanistic reasons for the lower exposure in oncology patients are not clear. A sensitivity popPK analysis was conducted by the reviewer where PK data from oncology patients were excluded, and the estimates of PK parameters are similar after excluding PK data from oncology patients.

Table 3: Impact of weight on Mean (%CV) Steady State Teprotumumab Exposure in All Patients

Characteristics		Weight quartiles			
		Q1	Q2	Q3	Q4
No. of subjects (%)		21 (25.3)	21 (25.3)	20 (24.1)	21 (25.3)
AUC_{ss} (µg*hr/mL)		112762 (20.6)	130650 (22.9)	131472 (23)	137394 (23.6)
$C_{max,ss}$ (µg/mL)		571.73 (17.3)	612.44 (22.3)	657.19 (19.3)	687.06 (18)
$C_{min,ss}$ (µg/mL)		136.33 (28.7)	158.75 (33)	152.95 (32)	150.41 (33.6)
Sex, N (%)	Male	1 (4.8)	4 (19)	6 (30)	15 (71.4)
	Female	20 (95.2)	17 (81)	14 (70)	6 (28.6)

Source: Applicant's popPK report, Table 11, Page 48

Table 4: Impact of Disease on Mean (%CV) Steady State Teprotumumab Exposure in All Patients

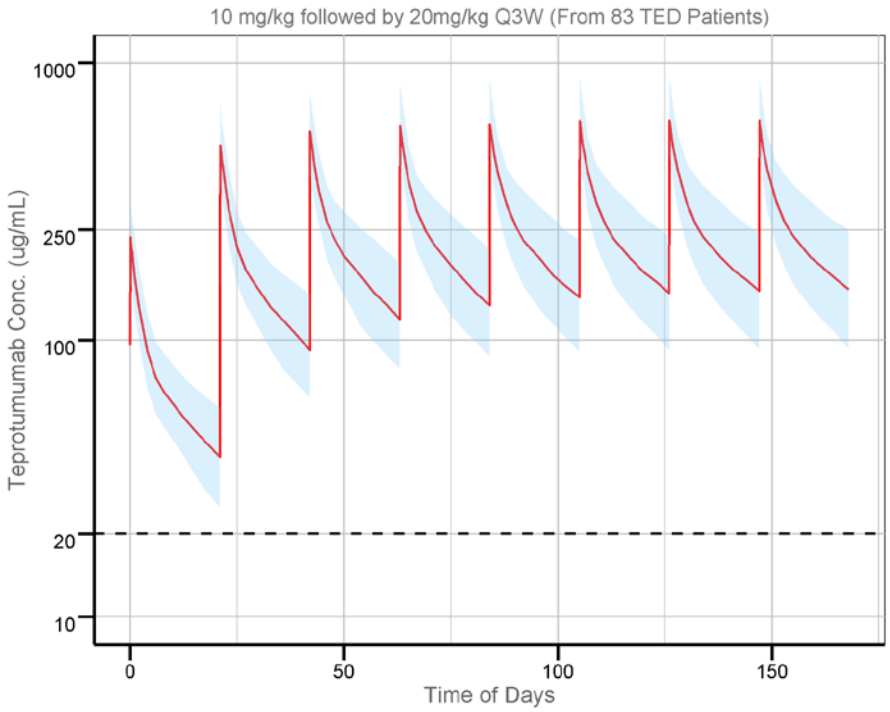
Characteristics		Disease			
		Oncology	TED		
			All patients	TED01RV	HZNP-TEP-301
No. of subjects (%)		36 (30.3)	83 (69.7)	43 (51.8)	40 (48.2)
AUC_{ss} (µg*hr/mL)		72715 (46.8)	127679 (23.6)	125738 (22.3)	129798 (24.9)
$C_{max,ss}$ (µg/mL)		416.75 (28.0)	630.26 (20.2)	647.63 (17.2)	612.10 (23.3)
$C_{min,ss}$ (µg/mL)		69.13 (71.1)	149.34 (32.2)	141.35 (30.5)	158.42 (32.8)
Sex, N (%)	Male	21 (58.3)	26 (31.3)	15 (34.9)	11 (27.5)
	Female	15 (41.7)	57 (68.7)	28 (65.1)	29 (72.5)

Source: Applicant's popPK report, Table 20, Page 44

Simulation was conducted to predict concentration-time profile of teprotumumab and exposure parameters after one dose of 10 mg/kg followed by 7 repeated doses of 20 mg/kg Q3W in TED patients (Figure 6). The median Cmin_ss was 151.8 (range: 65.6-307.7) mcg/mL and the median Cmin at first cycle was 37.8 mcg/mL (range: 21.9-38.5) mcg/mL. According to the Applicant, 20 µg/mL of teprotumumab concentrations in serum would result in >90% saturation of target-mediated clearance of teprotumumab (implying >90% saturation of IGF-1R). The popPK analysis on data from TED01RV and HZNP-TEP-301 studies confirmed that this selected regimen (one dose of 10 mg/kg followed by 7

repeated doses of 20 mg/kg Q3W) achieved serum trough concentrations consistently above 20 µg/mL in all TED patients. The rationale of the lower initial dose followed by doubled repeated dose is not justified by the Applicant or by the Clinical Pharmacology review team's exposure-response analyses for efficacy and safety. However, given this dosing regimen is efficacious, the dosing regimen is acceptable.

Figure 6: Simulated Teprotumumab Concentration-time Profile After First Doses of 10 mg/kg Followed by 7 Repeated Doses of 20 mg/kg Q3W in TED Patients



Source: Reviewer's Analysis to confirm Figure 12 in Applicant's popPK report

As PK samples collected from Study TED01RV were analyzed outside the established long-term stability period, a sensitivity analysis was conducted to derive PK parameter estimates without the PK data from Study TED01RV. The findings from this analysis suggested no significant impact (<6% difference) on the PK estimates for 40 patients in Study HZNP-TEP-301 (Table 5).

Table 5: Summary of PK estimates for 40 patients in Study HZNP-TEP-301based on PopPK analysis with and without PK data from study TED01RV

Exposure Parameter	Mean (SD) Estimates		Unit
	All PK Data	Without Study TED01RV PK Data	
AUC_ss	134.3 (33.4)	138.4 (33.5)	mg•hr/mL
Cmax_ss	622.4 (144.2)	631.9 (138.6)	mcg/mL
Cmin_ss	167 (54.7)	176.2 (56.2)	mcg/mL

Ss: Steady state at week 21 to 24

Source: Reviewer's Analysis based on "pkinput.csv"

4.4 Exposure Response Analysis

1) Methods and Data

Exposure-response analyses were conducted by the applicant to explore the relationship between exposure of teprotumumab and efficacy and safety in TED patients who received teprotumumab.

The selected efficacy endpoints included: Week 24 proptosis responder rate (PRR), diplopia response rate, and CAS response rate. See Section 4.2 for definition/criteria used for determining response rates. Exposure-efficacy relationship was evaluated in 83 patients with TED.

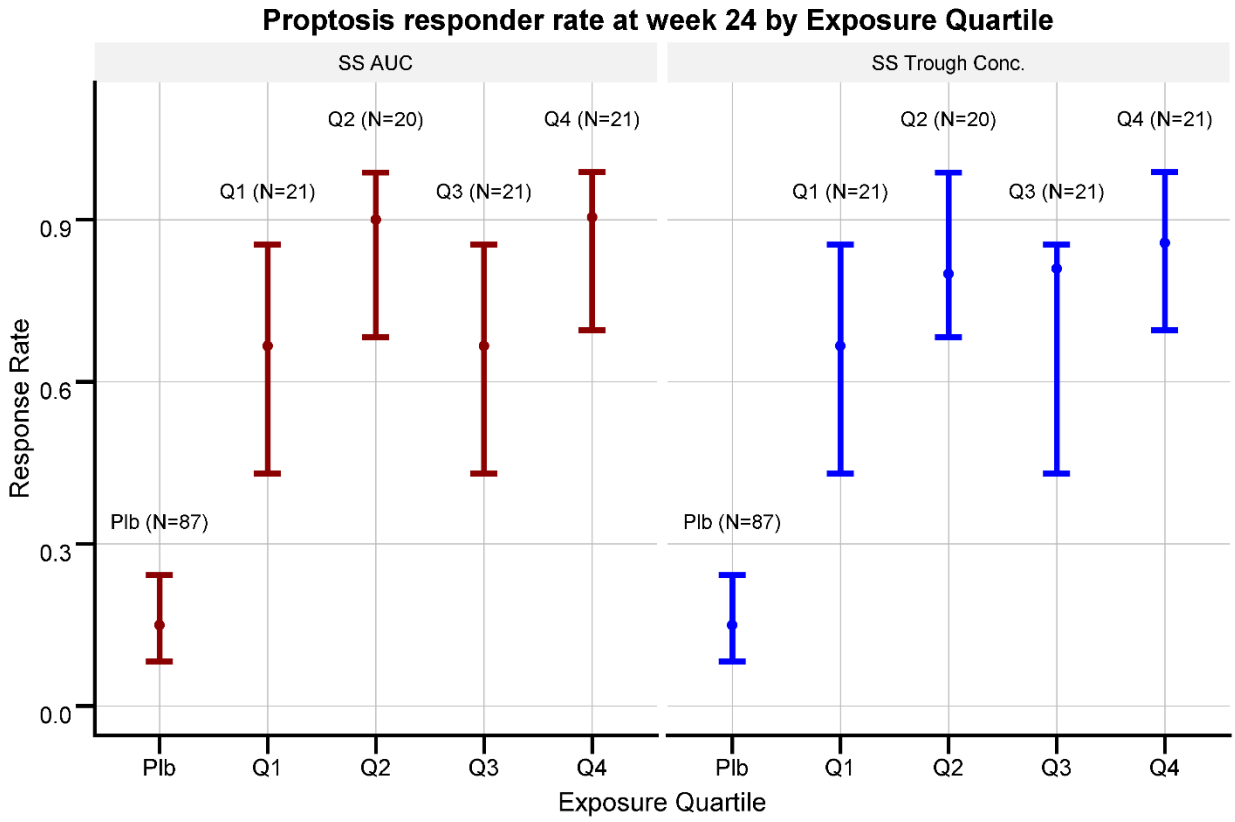
Exposure safety analyses were performed to investigate whether the adverse events could be attributed to the variability in teprotumumab exposure. The safety endpoints analyzed in the report were hyperglycemia and muscle spasm. The exposure-safety analyses were conducted in 84 patients from studies TED01RV and HZNP-TEP-301.

The primary exposure metrics for exposure-efficacy assessment are individual predicted teprotumumab exposure parameters at steady state: AUC_ss, Cmin_ss, Cmax_ss. These individual exposure metrics were calculated based on empirical Bayes estimates of individual PK parameters from previously developed final popPK model. The primary exposure metrics are AUC_ss and Cmax_ss for exposure-safety assessment and AUC_ss and Cmin_ss, for exposure-efficacy evaluation. Graphical quartile analyses were used to investigate the exposure-efficacy and exposure-AE relationships.

2) Exposure-efficacy relationship

Overall, there appear to be no conclusive trend of exposure-PRR relationship in 83 patients with TED. Patients in the first Cmin_ss quartile had the lower PRR compared to higher Cmin_ss quartiles. However, this relationship was not statistically significant, and PRR in all Cmin_ss quartiles was much higher than the PRR in placebo-treated patients. In addition, similar relationship was not observed in the quartile analysis between AUC_ss and PRR (Figure 7). The baseline covariates across all exposure quartiles in the exposure-PRR analyses appeared to be balanced (Table 6). Sex, baseline age, and smoking status, which are all reported to be risk factors for TED, were not found to be correlated with efficacy endpoints, although this analysis was limited in its small sample size based on a single dosing regimen. Similarly, no conclusive trend of exposure-efficacy relationships was observed for endpoints Week 24 diplopia response and Week 24 CAS response.

Figure 7: Relationship Between Teprotumumab Exposure and PRR in Patients with TED



Source: Reviewer's Analysis based on "efficacy.xpt".

Table 6: Distribution of Baseline Covariates Across Exposure Quartiles in the Exposure-Efficacy Relationship

Covariate	value	AUC Q1	AUC Q2	AUC Q3	AUC Q4
Number of Patients		21	20	21	21
Age (Years)		50.1 (11.4)	48 (11.2)	52 (11.5)	55 (12.2)
Body Weight (Kg)		66.5 (22.3)	74 (16.1)	82.3 (17.9)	78.5 (16.1)
Sex	Male	4 (19%)	8 (40%)	12 (57.1%)	2 (9.5%)
	Female	17 (81%)	12 (60%)	9 (42.9%)	19 (90.5%)
Smoking Status	Non-user	12 (57.1%)	17 (85%)	17 (81%)	17 (81%)
	User	9 (42.9%)	3 (15%)	4 (19%)	4 (19%)
Covariate	value	CMIN Q1	CMIN Q2	CMIN Q3	CMIN Q4
Number of Patients		21	20	21	21
Age (Years)		50.1 (12)	46.5 (11.3)	53 (10.3)	55.4 (12.1)
Body Weight (Kg)		73.5 (22.5)	79.8 (18.2)	78 (17.6)	75 (15.2)
Sex	Male	5 (23.8%)	8 (40%)	10 (47.6%)	3 (14.3%)
	Female	16 (76.2%)	12 (60%)	11 (52.4%)	18 (85.7%)
Smoking Status	Non-user	12 (57.1%)	17 (85%)	16 (76.2%)	18 (85.7%)
	User	9 (42.9%)	3 (15%)	5 (23.8%)	3 (14.3%)

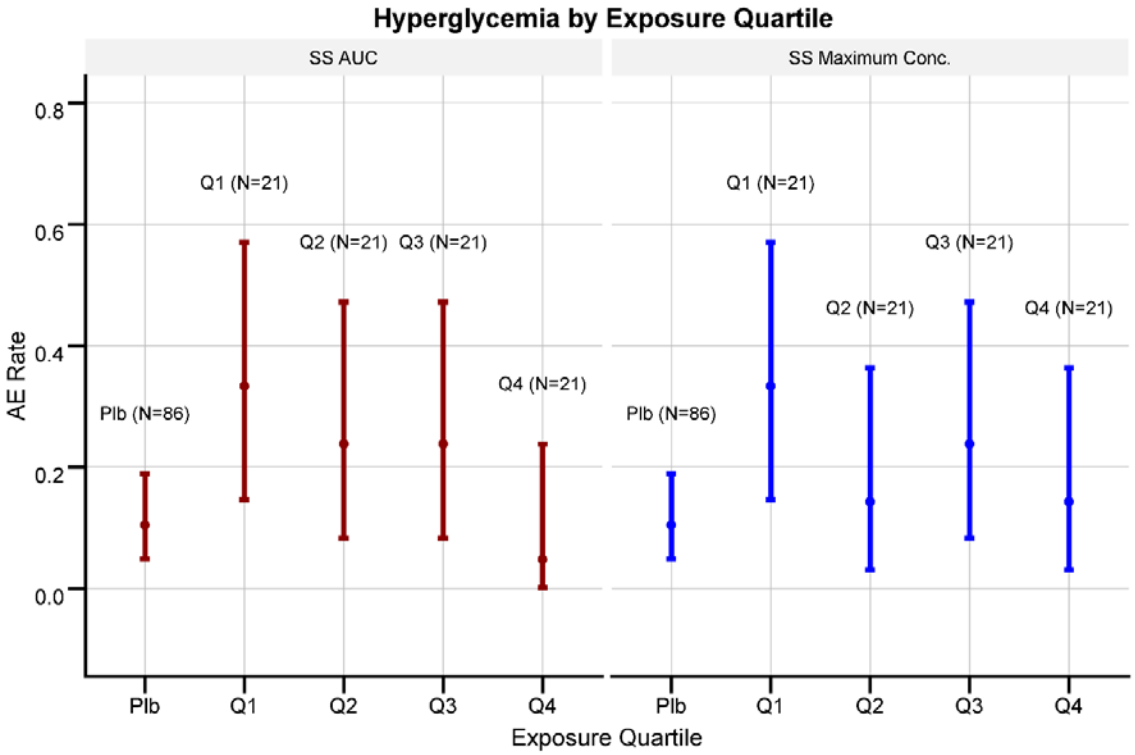
Source: Reviewer's Analysis based on "efficacy.xpt".

3) Exposure-safety Relationships

The probability of hyperglycemia by quartiles of AUC_ss or Cmax_ss is shown in Figure 8. No meaningful E-R relationship was observed for hyperglycemia using data collected from clinical studies HZNP-TEP-301 and TED01RV (n=84). There was a slight trend of lower incidence of hyperglycemia with increasing AUC_ss and Cmax_ss, which was not clinically meaningful. Similarly, the probability of muscle spasm by quartiles of AUC_ss or Cmax_ss is shown in Figure 9. No meaningful E-R relationship was observed for muscle spasm using data collected from 84 patients. The baseline covariates across all exposure quartiles in the exposure-efficacy analyses appeared to be balanced (Table 7). The exposure-safety relationship should be interpreted with caution as it is based on a small number of subjects from a single dosing regimen.

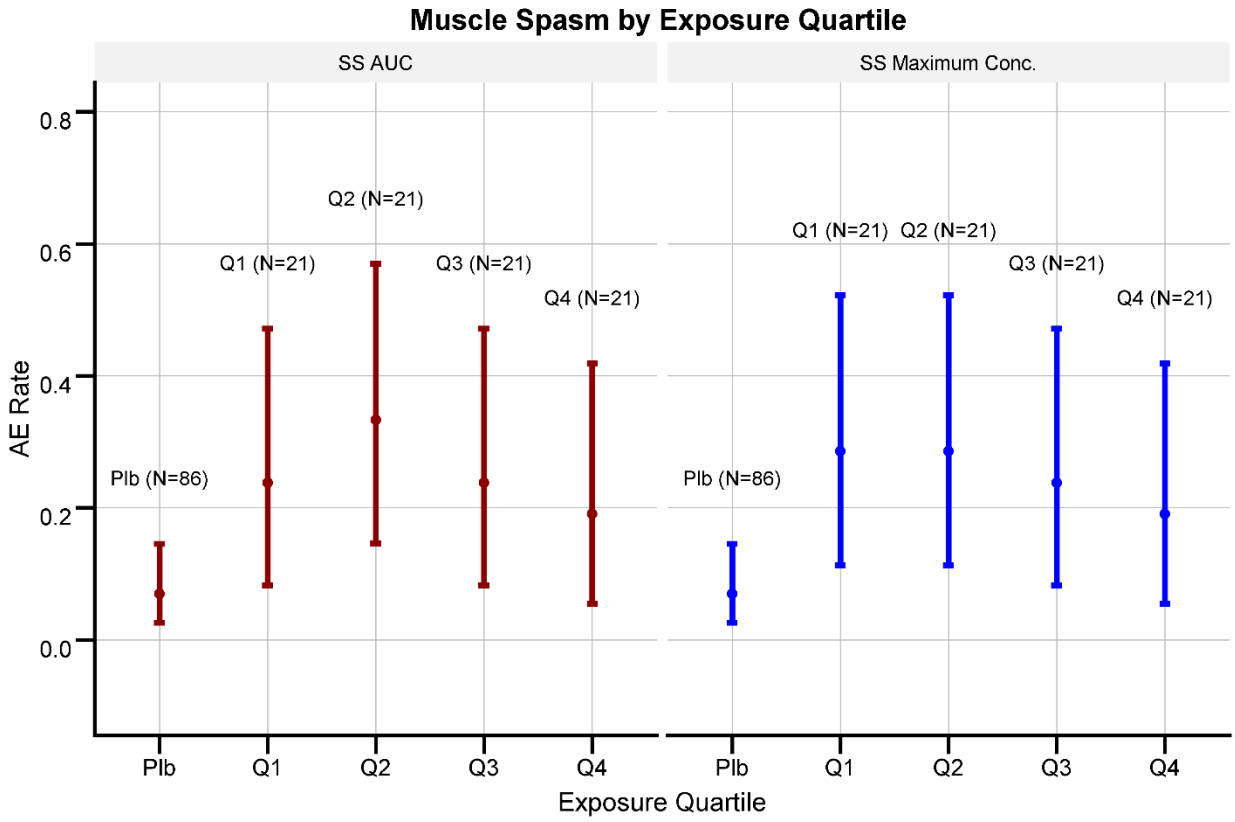
Patients with pre-existing diabetes were identified to have a higher probability of experiencing hyperglycemia. 5 of 10 (50%) patients with pre-existing diabetes experienced hyperglycemia after treatment of teprotumumab, which is much higher than the probability in patients without pre-existing diabetes (13/74, 17.6%).

Figure 8: Relationship Between Teprotumumab Exposure and Hyperglycemia



Source: Reviewer's Analysis based on "safety.xpt".

Figure 9: Relationship Between Teprotumumab Exposure and Muscle Spasm



Source: Reviewer's Analysis based on "safety.xpt".

Table 7: Baseline Covariates Across Exposure Quartiles in the Exposure-Safety Analyses

Covariate	value	AUC Q1	AUC Q2	AUC Q3	AUC Q4
Number of Patients		21	21	21	21
Age		50.1 (11.4)	47.9 (10.9)	52 (12.3)	55 (11.3)
Body Weight		66.5 (22.3)	74 (17.3)	80 (17.2)	79.8 (25)
Sex	Male	4 (19%)	9 (42.9%)	11 (52.4%)	3 (14.3%)
	Female	17 (81%)	12 (57.1%)	10 (47.6%)	18 (85.7%)
Smoking Status	Non-user	12 (57.1%)	18 (85.7%)	16 (76.2%)	18 (85.7%)
	User	9 (42.9%)	3 (14.3%)	5 (23.8%)	3 (14.3%)
Covariate	value	CMAX Q1	CMAX Q2	CMAX Q3	CMAX Q4
Number of Patients		21	21	21	21
Age		50.5 (13.8)	50.1 (9.4)	47.9 (10.5)	55.4 (12.1)
Body Weight		72 (16)	73.9 (18.4)	75 (22.5)	82.2 (23.8)
Sex	Male	6 (28.6%)	9 (42.9%)	9 (42.9%)	3 (14.3%)
	Female	15 (71.4%)	12 (57.1%)	12 (57.1%)	18 (85.7%)
Smoking Status	Non-user	15 (71.4%)	17 (81%)	15 (71.4%)	17 (81%)
	User	6 (28.6%)	4 (19%)	6 (28.6%)	4 (19%)

Source: Reviewer's Analysis based on "safety.xpt".

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PHILIP M COLANGELO
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JOHN A LAZOR
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